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14. ABSTRACT A retrospective case-cohort study was formed with 48,762 children with Autistic Spectrum Disorders (ASD) aged 2-18 years enrolled in the Military Health System from 2000-13. Children with ASD were matched 1:5 by age, gender, and enrollment time to children without ASD. International Classification of Diseases, 9th Revision, Clinical Modification and Current Procedural Terminology codes were extracted to examine associations and co-morbidities. Of perinatal conditions, seizures in the first 90 days of life were most highly associated with ASD. Specific seizure types such as absence seizures and infantile spasms have high associations with ASD, with children with ASD 4 times more likely to have seizures labeled as intractable. Seizures also account for most of the 17% increase in injury risk. Obesity and its complications are twice as common in children with ASD. However, children with ASD also are at risk for deficiencies in macro- and micronutrients, such as iron and vitamin D. Other comorbid conditions can be masked by ASD and lead to complications of missed or late diagnoses. Eosinophilic esophagitis is most strongly associated with a feeding disorder and not with ASD itself. Children with ASD who develop appendicitis are more likely to have perforation and sepsis, and those with otitis media are more likely to have perforation and cholesteatoma. Sleep disorders have a prevalence of 30% in children with ASD, and they are more likely to undergo procedures for their sleep issues. ASD is associated with multiple conditions throughout childhood, and the presence of ASD affects how clinicians diagnose and treat these conditions. These results provide clinicians with data to better screen and manage ASD patients.

15. SUBJECT TERMS
Autism, epidemiology, risk factors, co-morbidities

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INTRODUCTION:

This award funded the project entitled "Risk Factors, Comorbid Conditions, and Epidemiology of Autism in Children." The research team of pediatric specialists and researchers aims to understand contributing factors and associated condition with Autism Spectrum Disorders (ASD) using the military healthcare database. This medical system is unique in the United States in terms of the size of the population, its universal-coverage, open-access model, and its unified comprehensive electronic medical and demographic records. The researchers examined the medical records of children diagnosed with ASDs longitudinally over time in comparison to a large group of children without ASD. The researchers also linked children's medical records to their mothers to determine if there are temporal associations between childhood ASD and pre-natal and post-natal conditions such as infections, pregnancy-related conditions, and perinatal conditions such as jaundice and infection. In addition, the researchers examined records of children with ASD to determine the extent of co-morbid conditions and the use of medications.

KEYWORDS: Autism, epidemiology, risk factors

1. ACCOMPLISHMENTS:

What were the major goals of the project?

The Military Autism Research Group has two specific aims: evaluating and quantifying prenatal & perinatal risk factors for the subsequent development of ASD, and evaluating and quantifying co-morbid medical and behavioral conditions in children previously diagnosed with ASD. These aims were met by completing the following tasks on the following three-year timeframe which included a 12 month no-cost extension.

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What was accomplished under these goals?

1) major activities

- Confirmed association between ASD and neonatal jaundice using a more rigorous definition of exposure than that used in previous studies
- Documented increased risk of celiac disease in patients with ASD using procedurally and serological data
- Determined increased risk of complications from otitis media in patients with ASD
- Quantified psychotropic medication burden of children with ASD

- Determined increase in sleep-disorders in children with ASD
- Quantified the risk of macro- and micro-nutrient deficiencies in children with ASD
- Documented increased odds of obesity and components of metabolic syndrome in patients with ASD
- Documented multiple perinatal risk factors associated with later development of ASD

2) specific objectives

Task 1: Site: USUHS - Receive IRB approval of Military Autism Research Group project protocol (months 1-5)

1a. Generate criteria for selection of control group for inclusion in submissions to IRB and Tricare Data Use Agreement (month 1)

Completed in FY13.

1b. Complete IRB application and submit to USUHS IRB (month1)

Completed in FY13.

1c. Complete Data Use Agreement (DUA) and submit to TriCare Management Authority (month 1)

Completed in FY13. Renewed in FY14.
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1d. Coordinate with IRB, provide additional materials as needed and respond to questions (months 2-4)

Completed in FY13.

1e. Receive IRB approval for Military Autism Research Group project (month4).

Completed in FY13. Continuing review submitted and approved in September 2014

1f. Submit local USUHS IRB approval letter to Department of Defense, Health Research Protection Office (HRPO) for secondary protocol review and approval (month 4)

Completed in FY13.

1g. Finalize Data Use Agreement with TriCare Management Authority (month 5).

Completed in FY13.

1h. Receive HRPO IRB approval (month 5)

Completed in FY13.

Task 2: Procure hardware and software equipment, and configure components for use in data downloads, cleaning and analysis. (months 1-5)

2a. Purchase Computer Server (month 1-2)

New hardware was purchased.

2b. Purchase Computer Software (month 1-2)

Software was obtained.

2c. Link Computer Server with desktop computers used for data analysis and cleaning (months 2-5)

Completed.

2d. Load computer software onto computers for use in data analysis (months 2-5).

Completed.

Task 3: Download data from the Military Health Services (MHS) Management Analysis and Reporting Tool (M2) (month 6-9)

3a. Use established criteria to generate a list of control group members. (month 6-7)

Completed in FY13

3b. Identify electronic data interchange patient number (EDIPN), a unique identifier common to Department of Defense databases for experimental and control groups. (month 6-7)

Completed in FY13.

3c. Identify mothers of experimental and control group identified children, of appropriate age to accurately identify prenatal & perinatal risk factors. (month 6-7)

Using the sponsor EDIPN field of included cases and controls and the '30' Family Member Prefix (FMP), we identified individuals in the SADR database assumed to be the biological mother and extracted records. We then requeried the SADR and SIDR Inpatient database for all records in the 24 months prior to and 6 months after the birthdate of the case or control.

3d. Download all health care visit and medication data for identified experimental and control group members. (month 7-9)

All outpatient health care visits were downloaded from the SADR database. Filters for targeted conditions such as otitis media, celiac disease, appendicitis, injuries, obesity and its complications (hypertension, hyperlipidemia), and sleep disorders have been chosen for analysis. Specific medications downloaded include psychotropic medications and antibiotics.

3e. Download all health care visit and medication data for perinatal period for experimental and control group mothers. (month 7-9)

Maternal health data and medication use in the prenatal and perinatal period was obtained.

Task 4: Cleaning & Organization of Data, and Data Analysis (months 10-17)

4a. Convert downloaded data to format for use by Stata Statistical Software (month 10-11)

Completed in FY13.

4b. Use established criteria to identify mothers with research indicated prenatal or perinatal risk factors, and create database flags (month 11-12)

Multiple criteria generating a flag for future analysis were identified, including (1) use of a psychotropic medication prenatally and (2) maternal mental health diagnoses.

4c. Use established criteria to identify subjects with research indicated co-morbid conditions (months 11-12)

Co-morbid conditions of celiac disease, sleep-disordered breathing, obesity, hypertension, appendicitis, hyperlipidemia, non-alcoholic steatohepatitis, psychiatric conditions, tonsillectomy/adenoidectomy, otitis media, epilepsy, mental health conditions, and maternal perinatal infections were identified.

4d. Merge Health Care utilization data with parental data provided to the research team by the Defense Manpower Data Center. Data will include: parental deployment history, rank, age, gender and other demographic characteristics. (months 11-13)

Deployment history was not obtained. Parent demographic data was obtained through the MDR database.

4e. Write code for analysis of data. (months 13-15)

A full-time research assistant with SAS and UNIX programming skills was hired in April 2014. Code has been written for multiple analyses. A master extraction algorithm was written that accounts for the variation of the same data field across fiscal years.

4f. Run statistical analysis, analyze results and refine analysis as appropriate (months 15-17)

Analyses have been completed for all aims. See annotated bibliography (Appendix)

4g. Interpret results of data analysis in the clinical context of Autism care (months 15-17)

Interpretations have been completed for all aims. See bibliography (Appendix 1).

4h. As results emerge, create and submit abstracts for presentation at medical conferences (months 15-17)

See bibliography (Appendix 1).

Task 5: Present and Write up research results (months 18-24)

5a. Create presentations and posters for presentation at medical conferences (months 18-20)

See bibliography (Appendix 1).

5b. Present findings at medical conferences (months 18-24)

Peer-reviewed research has been presented in abstract form at the following medical conferences:

- Society for Developmental and Behavioral Pediatrics, Las Vegas, NV, Oct 2015
- Pediatric Academic Society Annual Meeting, Vancouver, BC, May 2014
- Society for Developmental and Behavioral Pediatrics, Nashville, TN, Sept 2014

5c. Draft manuscripts for publication (months 18-24)

Four manuscripts have been submitted for publication

5d. Finalize papers and submit to pediatric medical journals (months 20-24)

See 5d above.

3) Major Findings

During the last fiscal year, the research group focused on obesity, sleep disorders, seizures, mental health diagnoses, medication burden, injuries, management of acute conditions such as otitis media and appendicitis, feeding concerns including malnutrition and eosinophilic esophagitis, and perinatal risk factors.

OBESITY: This project documented and quantified the risk of obesity and its complications. There is almost a two-times increase in the odds of a child with ASD developing obesity complications (Table 1 and Figure 1). Children with ASD are also at increased odds of being prescribed medications for metabolic syndrome complications (Table 2). Several classes of medications, including mood-stabilizers, SSRIs, anti-psychotics, and anti-epileptics, are also associated with obesity in children with ASD (Table 3).

Table 1. Incidence and Odds Ratios for Diagnosis of Obesity and Obesity-related Metabolic Disorders for Children with ASD Compared to Controls

	ASD (n=48,762)	**Control (n=243,810)**	**Odds Ratio (95% CI)**
Obesity	4,004 (8.2%)	11,402 (4.7%)	1.85 (1.78-1.92)
Type 2 Diabetes Mellitus	515 (1.1%)	970 (0.4%)	2.68 (2.41-2.99)
Hypertension	497 (1.0%)	1,227 (0.5%)	2.04 (1.84-2.27)
Hyperlipidemia	1,606 (3.3%)	4,085 (1.7%)	2.01 (1.90-2.13)
NAFLD/NASH	73 (0.2%)	133 (0.1%)	2.74 (2.06-3.)

Figure 1. Percentage of Patients with Obesity and Metabolic Disorders among Children with ASD and Controls

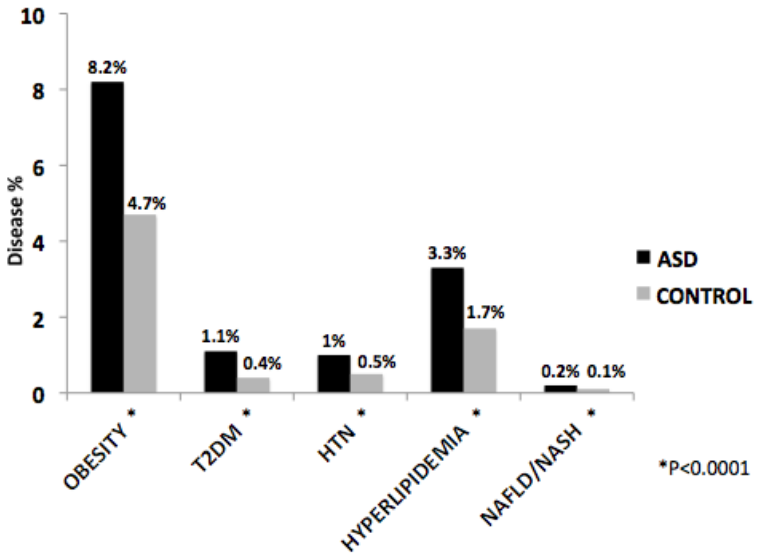


Table 2. Incidence and Odds Ratios of Prescription Treatment for Obesity-Related Metabolic Disorders in Children with ASD Compared to Controls among Those with Each Condition

	Total Children with ASD and Condition	**Children with ASD and Treated for Condition**	**Total Controls with Condition**	**Controls with Condition and Treated for Condition**	**Relative Risks (95% CI)**
Type 2 Diabetes	515	68 (13.2%)	970	83 (8.6%)	1.54 (1.14-2.09)
Hypertension	497	226 (45.5%)	1227	470 (38.3%)	1.19 (1.05-1.34)
Hyperlipidemia	1606	99 (6.2%)	4085	146 (3.6%)	1.72 (1.35-2.21)

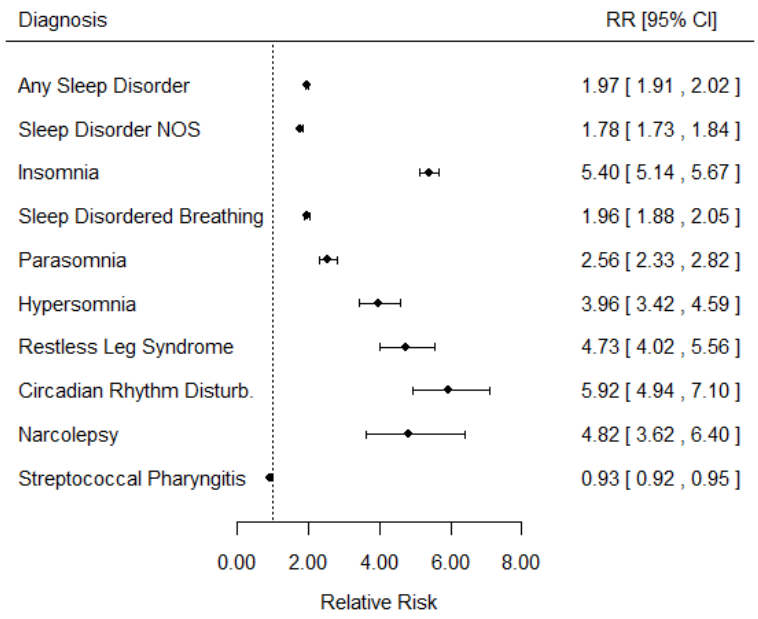
Table 3: Odds Ratios of Obesity among Children with ASD.

	ASD Mean Days (SD)	**Unadjusted Odds Ratio (95% CI)**	**Adjusted Odds Ratios (95% CI)**
Mood Stabilizers	12.7 (134.2)	2.00 (1.72, 2.33)	1.41 (1.19, 1.66)
Anti-Psychotics	74.8 (349.0)	1.22 (1.19, 1.24)	1.16 (1.13, 1.19)
Anti-Epileptics	60.4 (324.9)	1.19 (1.16, 1.22)	1.14 (1.11, 1.17)
SSRIs	84.3 (327.3)	1.18 (1.15, 1.21)	1.13 (1.10, 1.16)
ADHD	650.6 (1161.8)	1.03 (1.02, 1.04)	1.01 (0.99, 1.02)
Tricyclics	2.9 (42.2)	1.13 (0.93, 1.37)	0.96 (0.76, 1.20)
Alpha Agonists	39.4 (167.7)	0.97 (0.92, 1.03)	0.90 (0.84, 0.96)

Medications were included in the logistic regression model as continuous variables utilizing a unit change representing a 10% increase in days prescribed out of total days enrolled. CI= confidence interval.

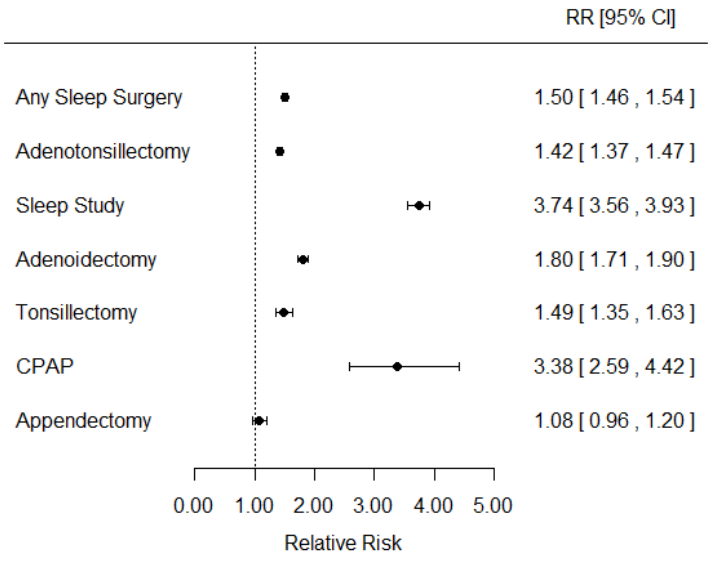
SLEEP DISORDERS: Sleep disorder prevalence is approximately 30% in children with ASD – one of the most common co-morbid conditions (Table 4). Children with ASD have a much higher rate of sleep disorders (Figure 2), and undergo procedures for sleep-disordered breathing at a higher rate than children without ASD (Figure 3). With the knowledge of this population-generated mean age of diagnosis between 6 and 10 years of age, clinicians can use this data to screen children with ASD to diagnose and intervene earlier.

Figure 2: Relative risk for sleep disorder diagnoses in children with vs. without autism.



RR adjusted for matching variables of gender and birthyear, and the covariate total number of outpatient encounters. Streptococcal pharyngitis is included as the control diagnosis.

Figure 3: Relative risk for sleep related procedures in children with vs. without autism.



Appendectomy is included as a control procedure.

Table 4: Prevalence and mean age of sleep disorder diagnoses and sleep related procedures in children with autism as compared to matched controls.

	ASD (n=48,762)		Controls (n= 243,810)		Comparison of mean ages
Diagnosis	**Children with diagnosis (%)**	**Mean Age of Diagnosis (SD)**	**Children with diagnosis (%)**	**Mean Age of Diagnosis (SD)**	**p-value**
Circadian rhythm disorder	304 (0.62)	8.32 (4.31)	219 (0.09)	9.75 (5.07)	<0.01
Hypersomnia	367 (0.75)	10.55 (4.64)	412 (0.17)	10.78 (4.57)	0.69
Insomnia	4643 (9.52)	8.84 (4.21)	3861 (1.58)	11.03 (4.32)	<0.01
Narcolepsy	105 (0.22)	12.19 (3.79)	97 (0.04)	12.57 (3.96)	0.49
Parasomnias	741 (1.52)	6.35 (3.59)	1255 (0.51)	6.36 (3.52)	0.99
RLS	336 (0.69)	9.63 (4.30)	310 (0.13)	10.09 (4.30)	0.20
Sleep Disordered Breathing	4514 (9.26)	7.20 (4.05)	9928 (4.07)	6.57 (3.62)	<0.01
Sleep Disorder NOS	10593 (21.72)	7.03 (4.00)	26263 (10.77)	7.07 (4.02)	0.22
Any Sleep Disorder	14951 (30.66)	7.19 (4.09)	33937 (13.92)	7.21 (4.14)	0.28
Streptococcal Pharyngitis	13199 (27.07)	7.11 (3.29)	67244 (27.58)	7.01 (3.34)	0.01
Procedure	**Children having had procedure (%)**	**Mean Age at Time of Procedure (SD)**	**Children having had procedure (%)**	**Mean Age at Time of Procedure (SD)**	**p-value**
Polysomnography	2633 (5.40)	8.63 (4.30)	3517 (1.44)	8.41 (4.20)	0.13
CPAP	90 (0.18)	8.90 (4.99)	133 (0.05)	7.99 (4.63)	<0.01
Tonsillectomy	549 (1.13)	7.60 (4.03)	1847 (0.76)	8.51 (4.38)	<0.01
Adenotonsillectomy	3908 (8.01)	6.22 (3.10)	13771 (5.65)	6.38 (3.06)	<0.01
Adenoidectomy	1920 (3.94)	4.91 (2.67)	5321 (2.18)	5.16 (2.72)	<0.01
Sleep surgery	6035 (12.38)	6.03 (3.33)	20130 (8.26)	6.37 (3.38)	<0.01
Appendectomy	380 (0.78)	10.75 (3.56)	1766 (0.72)	10.89 (3.59)	0.46

Comparisons are made between least squares (LS) mean ages accounting for match with associated p-values reported. RLS= Periodic limb movement disorder/restless leg syndrome, CPAP= Continuous Positive Airway Pressure, NOS= Not Otherwise Specified, Sleep surgery= all sleep-related otolaryngologic surgeries combined

OTITIS MEDIA: Children with ASD are more likely to be diagnosed with otitis media, one of the most common reasons for acute visits in primary care pediatric practice. They undergo surgery for pressure equalization tubes at a higher rate than the general pediatric population, and have approximately twice the risk of complications such as perforation and cholesteatoma (Table 5 & 6).

Table 5**.** Incidence density and incidence rate ratios of otitis media related visits and procedures

	Incidence density for autism spectrum disorders events per 100 person-years	**Incidence density for controls events per 100 person-years**	**Unadjusted IRR (95% CI)**	**Adjusted IRR (95% CI)**
Acute otitis media	4.78	4.25	1.41 (1.40-1.42)	1.27 (1.26-1.28)
Otitis media with effusion	2.17	1.62	1.66 (1.64-1.68)	1.50 (1.48-1.52)
Otorrhea	0.48	0.28	2.08 (2.02-2.13)	1.77 (1.72-1.82)
Pressure equalizer tube placement	0.73	0.35	2.22 (2.16-2.29)	1.93 (1.87-1.99)

Incidence rate ratios (IRR) with 95% confidence intervals (95% CI) were calculated using conditional Poisson regression. The adjusted model included a variable representing the total number of outpatient visits.

Table 6. Association of autism spectrum disorders with complications of otitis media

	ASD (N=48,762)	**Controls (N=243,810)**	**OR (95% CI)**
Cholesteatoma	202 (0.41%)	547 (0.23%)	1.85 (1.57-2.17)
Mastoiditis	239 (0.49%)	508 (0.21%)	2.35 (2.02-2.74)
Mastoidectomy	11 (0.023%)	24 (0.01%)	2.29 (1.12-4.68)
Tympanoplasty	9 (0.018%)	20 (0.008%)	2.25 (1.03-4.94)

Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated using conditional logistic regression without adjusting for the total number of outpatient visits**.**

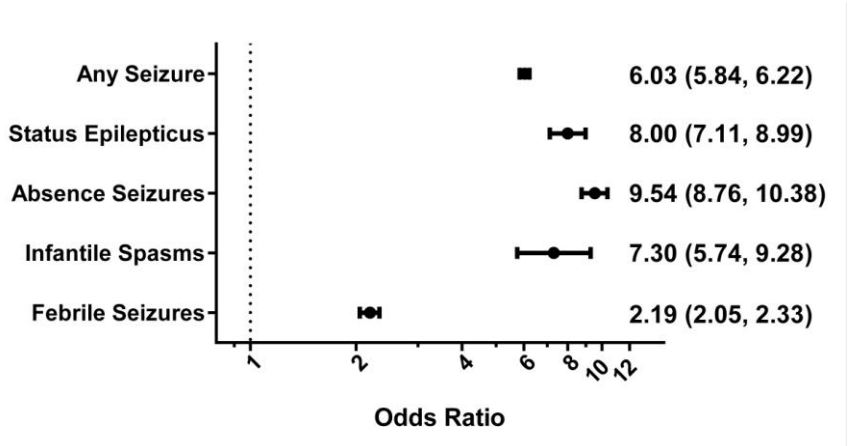
APPENDICITIS: There was no statistically significant difference in the rate of appendicitis based on ASD status. However, those with ASD had 1.06 (95% CI 0.95, 1.19) times the odds of appendicitis compared to those without ASD. After controlling for perforation, sepsis, and appendicitis age, ASD status was not a significant predictor in length of hospital stay (p-value 0.4558). Of children with ASD and appendicitis, 29% experienced perforation or peritonitis compared to 25% of controls with appendicitis. Children with ASD 0-14 years of age did not have an increased rate of perforation, however children 15-17 did (Table 7) After controlling for age of appendicitis and perforation/abscess, those with ASD had 3.79 (95% CI 1.37, 10.46) times the odds of having secondary sepsis when compared to those without ASD.

Table 7. Observed Rate of Perforation/Peritonitis per 1,000 Inpatient Admissions for Appendicitis

	ASD Observed Rate per 1,000	No ASD Observed Rate per 1,000	AHRQ Benchmark Observed Rate per 1,000
All Ages (0-17)	290.6	252.6	305.2
0-4 years	416.7	546.9	627.1
5-9 years	260.6	271.4	361.0
10-14 years	298.1	221.7	286.9
15-17 years	290.9	157.5	213.8
Males	285.7	247.2	306.9
Females	313.4	284.1	302.6

SEIZURES: Children with ASD are vastly more likely to have seizures of all different seizure types compared to children without ASD. Specific seizure types such as absence seizures and infantile spasms have high associations with ASD (Figure 6). They are 8 times more likely to receive a diagnosis of status epilepticus, and 12 times more likely to have an inpatient hospital stay compared to children without ASD. They are 4 times more likely to have seizures that are difficult to treat, and have been labeled as intractable.

Figure 6. Association of Archetypal Seizure Types with Autistic Spectrum Disorders



EOSINOPHILIC ESOPHAGITIS (EoE): EoE was more common in children with ASD (0.4%) compared to controls (0.1%). Feeding disorders were associated with EoE in both children with ASD and controls. Feeding disorders also had a higher odds ratio for EoE compared to other atopic conditions, among both children with ASD (7.17, 95% CI 4.87-10.5) and controls (11.5, 95% CI 7.57-17.5). Compared to controls with a feeding disorder, children with ASD and a feeding disorder had no difference in the rate of diagnosed EoE (0.85, 0.95% CI 0.39-1.88). Feeding disorders associated with ASD should be considered as a risk factor for EoE as in any child with a feeding disorder.

MALNUTRITION: Despite the association with obesity and its complications, the study group found that children with ASD are also at risk for specific macro and micronutrient deficiencies (Figures 5 and 6)

Figure 4: Incidence of Failure to Thrive, Iron Deficiency Anemia, and Vitamin D Deficiency in Children with and Without Autistic Spectrum Disorders

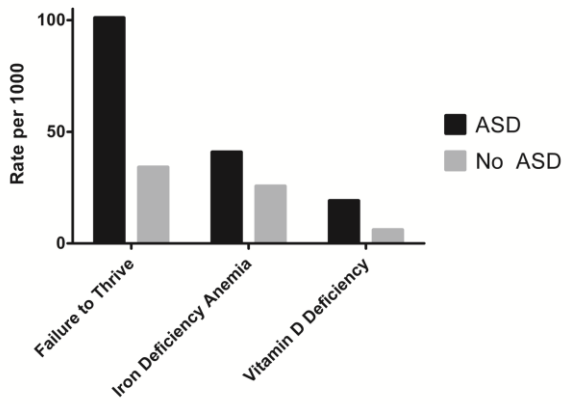
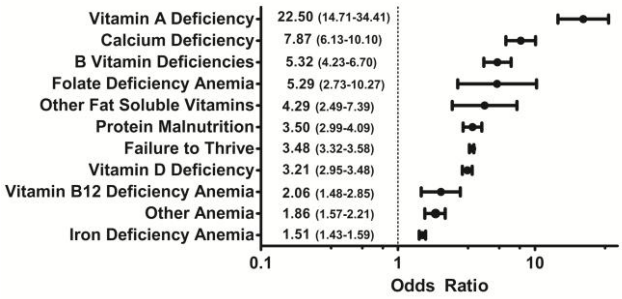


Figure 5: Relative Risk of Micronutrient Deficiencies in Children with and Without Autistic Spectrum Disorders



INJURIES: Children with ASD have a 17% increased rate of injury compared to controls without ASD. After adjusting for comorbid ADHD and epilepsy, the rate of all injuries is slightly decreased in children with ASD, however certain specific injuries including burns, poisoning, and environmental/inflicted injuries are increased in children with ASD (Table 8). As compared to healthy controls injuries increased with ASD (4%), ASD and ADHD (20%), ASD and epilepsy (160%) and ASD epilepsy and ADHD (103%) (Table 9).

Table 8: Adjusted Incidence Rate Ratio of Injuries in Children with ASD compared to Controls

	IRR [95% CI]
All Injuries	0.97 [0.96-0.97]
Joint	0.74 [0.71-.77]
Fracture	0.78 [0.77-0.79]
Spinal	0.90 [0.74-1.11]
Intracranial	0.78 [0.74-0.81]
Crushing	0.87 [0.82-0.93]
Open Wound	0.96 [0.95-0.98]
Sprains and Strains	0.63 [0.62-0.64]
Superficial	0.97 [0.96-0.98]
Burns	1.14 [1.08-1.19]
Complications	2.43 [2.36-2.50]
Poisoning	1.84 [1.79-1.89]
Other (i.e. environmental exposure, child maltreatment)	1.08 [1.07-1.10]

Table 9: Incidence Rate Ratio of Injuries in Children by Medical Condition

	IRR [95% CI]
Reference - No Autism, ADHD or Epilepsy	1.00
Autism	1.04 [1.03-1.05]
Autism and ADHD	1.20 [1.19-1.20]
Autism and Epilepsy	2.60 [2.55-2.65]
Autism, Epilepsy & ADHD	2.03 [2.00-2.06]

PERINATAL RISK FACTORS: Multiple perinatal conditions were evaluated. ASD was most highly associated with a neonatal seizure in the first 90 days of life, followed by maternal mental health diagnoses, epilepsy and obesity (Table 10).

Table 10: Adjusted Odds of Autism Based on Maternal & Neonatal Characteristics

Maternal & Newborn Historical Factors	**OR (95% CI)**
Maternal Infection	1.08 (1.03-1.14)
Birth Injury and Fetal Distress	1.15 (1.10-1.21)
Maternal Hypertension	1.20 (1.12-1.28)
Labor Complications	1.09 (1.04-1.16)
Pregnancy Complications	1.15 (1.08-1.21)
Gestational Diabetes	1.11 (1.03-1.19)
Short Gestation	1.14 (1.03-1.26)
Low Birth Weight	1.25 (1.11-1.41)
Maternal Autoimmune Disease	1.22 (1.03-1.45)
Assisted Fertility	1.22 (1.13-1.33)
Maternal Epilepsy	1.36 (1.01-1.84)
Maternal Obesity	1.26 (1.15-1.38)
Maternal Mental Health Diagnosis	1.50 (1.41-1.60)
Newborn Infection	1.15 (1.08-1.23)
Newborn Epilepsy	8.23 (6.20-10.94)

MEDICATION BURDEN: This project documented the high medication burden associated with ASD. Of children with ASD 65% were prescribed one or more psychotropic medication as compared to 19% of controls (Table 11). Children with ASD were more likely be treated with all classes of psychotropic medications. Common comorbidities of ASD conferred increase medication burden with children who had ASD, epilepsy and a sleep disorder having over 32 times as many medication days as children with ASD alone (Table 12). Children with ASD and common comorbidities were also far more likely to be treated with multiple classes of psychotropic medications, as compared to controls (Table 13).

Table 11: Types of medications by therapeutic class prescribed to children with ASD and matched controls and Incidence Rate Ratio of days prescribed medication.

Therapeutic drug class	ASD (n=48810)	Control (n=244045)	Incidence Rate Ratio [95% CI]	Days prescribed per year	
				ASD	Control
All Included Medications	31,841 (65.3%)	45,740 (18.8%)	9.33 [9.33-9.33]	184.60	19.78
Stimulants	23,407(48.0%)	28444 (11.7%)	5.66 [8.25-8.67]	65.15	11.51
Non-Stimulant ADHD Medications	17,360 (35.6)	11,353 (4.7%)	12.16 [12.15-12.18]	30.63	2.52
Antipsychotics	14,850 (30.5%)	5,063 (0.00%)	25.51 [25.48-25.55]	33.60	1.32
Antidepressants	15,493 (31.8%)	12,977 (5.3%)	12.26 [12.25-12.27]	28.10	2.29
Anxiolytics	7,123 (14.6%)	6,127 (2.5%)	12.21 [12.17-12.25]	2.76	0.23
Anti-Epileptic	8,603 (17.6%)	5,902 (2.4%)	12.84 [12.83-12.86]	21.28	1.66
Mood Stabilizer	1,101 (2.3%)	386 (0.2%)	18.10 [18.00- 18.20]	1.43	0.08
Antiparkinson's	1,233 (2.5%)	377 (0.2%)	22.87 [22.69-23.04]	0.84	0.04
Muscle Relaxants	779 (1.6%)	4,933 (2.0%)	2.88 [2.86-2.90]	0.30	0.11
Alzheimer Medication	145 (0.3%)	10 (0%)	146.68 [140.17-153.49]	0.13	0.0009
Sleep Medication	833 (1.7%)	830 (0.3%)	9.48 [9.40-9.55]	0.38	0.04

ASD=Autism Spectrum Disorder, ADHD=Attention Deficit Hyperactivity Disorder

Table 12: Impact of Comorbid Conditions on Medication Days per Year in Children with Autism after Controlling for Gender, Age and Time Followed

	IRR	95% CI	p
Reference – Autism with no Comorbidity	1		
Any Mental Health Condition	12.95	12.92-12.99	<0.0001
Epilepsy	11.80	11.76-11.84	<0.0001
Sleep Disorder	1.86	1.85-1.87	<0.0001
Epilepsy & Any Mental Health Condition	24.01	23.94-24.08	<0.0001
Sleep Disorder & Any Mental Health Condition	20.01	19.96-20.07	<0.0001
Epilepsy & Sleep Disorder	32.56	32.47-32.65	<0.0001

Table 13: Percentage of children and number of medication by co-morbid conditions

	No Medications	1	2	3	≥4
No ASD	81.2	11.4	4.3	1.7	1.4
All Children With ASD	34.7	17.6	15.0	12.4	20.3
ASD and Any Mental Health Condition	23.2	19.1	17.7	15.0	25.0
ASD and Adjustment Disorders	16.3	15.5	17.1	17.1	34.1
ASD and Anxiety Disorders	14.2	13.4	16.7	17.6	38.2
ASD and Attention Deficit Disorders	15.3	19.3	19.2	17.0	29.3
ASD and Delirium/Dementia	14.6	15.0	14.8	14.3	41.3
ASD and Elimination, Tic Other	16.4	13.4	15.7	16.1	38.4
ASD and Impulse Control Disorders	5.3	7.2	10.2	15.2	62.2
ASD and Mood Disorders	7.0	9.7	14.1	19.2	50.0
ASD and Personality Disorders	6.0	7.0	8.9	14.2	64.0
ASD and Schizophrenia	3.2	4.7	9.2	14.6	68.3
ASD and Suicidal Ideation	3.1	5.0	9.6	16.0	66.4
ASD and Misc. Mental Health	24.4	15.9	16.2	14.8	28.7
ASD and Sleep Disorders	10.7	15.9	17.3	15.5	40.7
ASD and Epilepsy	21.0	15.1	16.5	15.9	31.6
ASD and No Diagnosed Comorbidities	87.2	8.6	2.4	1.1	.7

MENTAL HEALTH: Mental health conditions are likely the most common co-morbid conditions in children with ASD. Over 80% of children with ASD are diagnosed with one or more mental health condition as compared to matched controls (30%). ASD is associated with the greatest increase in odds of developing personality disorders, schizophrenia and impulse control disorders (Table 14). As compared to matched controls children with ASD are most likely to have multiple mental health diagnoses, be diagnosed at a younger age, have experienced a mental health hospitalization, and have a greater medication burden (Table 15).

Table 14: Odds Ratio of Mental Health Diagnoses in Children with and without ASD

	OR	95% CI
Any Mental Health Diagnosis	2.65	2.62-2.68
Adjustment Disorders	2.32	2.27-2.37
Anxiety	4.66	4.57-4.76
Attention Deficit Disorders	3.81	3.75-3.86
Delirium Dementia & Cognitive Disorders	5.18	4.90-5.48
Mutism, Tic & Emotional Disorders	3.87	3.76-3.97
Impulse Control	9.50	8.96-10.06
Mood Disorders	4.41	4.31-4.51
Personality Disorders	11.82	10.95-12.76
Schizophrenia	10.93	10.23-11.69
Suicidal	5.03	4.72-5.36
Somatoform, Dissociative & Eating Disorders	4.87	4.74-5.01

Table 15. Mental Health Indicators in Children with ASD and Matched Controls

	ASD	No ASD	p
Mean Number of MH Conditions	2.2	0.55	<0.001
Mean Age of First MH Diagnosis	6.8	8.5	<0.001
Mean MH Hospitalizations	0.2	0	<0.001
Mean Medication Days Per Year – Children with MH Diagnosis	200.3	18.7	<0.001
Mean Medication Days Per Year – Children without MH Diagnosis	56.4	1.2	<0.001

4) other achievements.

Three manuscripts have been submitted in September 2015: "Otitis Media and Related Complications among Children with Autism Spectrum Disorders," "Feeding Disorders in Children with Autism Spectrum Disorders Are Associated with Eosinophilic Esophagitis" and "Autism Spectrum Disorders and Metabolic Complications of Obesity."

Deployment data was not included. This was removed from the database to which we had access.

What opportunities for training and professional development has the project provided?

The project team involved multiple trainees in pediatric graduate medical education. These trainees gained proficiency in research methods, including operationalizing research definitions, basic biostatistical methods and use of professional statistical software, interpretation of results, and scientific writing. Project team members with advanced professional skills gained experience mentoring trainees.

Three trainees earned research awards through this project:

Dr. Katherine Shedlock, Pediatric Endocrine Society Special Recognition, Pediatric Academic Society Annual Meeting 2015

Dr. Katherine Shedlock, Navy-Wide Research Competition Clinical Research Award 1st Place, 2015

Dr. Jennifer Jaskiewicz, American Academy of Pediatrics Neurology Trainee Award, 2015

Dr. Luis E. Lozada, Society for Pediatric Research House Officer Research Award, 2013

How were the results disseminated to communities of interest?

Results were disseminated through peer-reviewed publications in journals, national, and regional research conferences.

What do you plan to do during the next reporting period to accomplish the goals?

Nothing to report.

IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

The size of our study population was quite large compared to prior studies on similar topics. Therefore, some of the research results confirm prior suspicions regarding associations and potential associations with Autism. The researchers found some very specific outcomes that will affect the way the pediatric primary care providers and developmental behavioral pediatricians will approach children with autism in the future. For example, more careful monitoring of newborns who have seizures in the first 90 days of life or hyperbilirubinemia requiring phototherapy for subsequent ASD diagnosis or screening children with ASD more carefully for sleep disordered breathing. Likewise this population is more likely to have ear infections and their complications, eosinophilic esophagitis, and perforation with appendicitis.

What was the impact on other disciplines?

Based on the aforementioned information, additional disciplines' practices could be affected. For example, ENT providers would benefit from understanding that there is increased incidence of ear infection complications; therefore, they may be more likely to place ear tubes sooner in children with ASD. Likewise, the pediatric/general surgeon may have a lower threshold for performing an appendectomy in a child with ASD with right lower quadrant pain. There is an increased incidence of obesity and metabolic syndrome in this population as well based on the results. This provides all the more reason to provide more intense and encompassing services regarding diet, exercise, and nutrition to this population, which is a multi-disciplinary task.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

CHANGES/PROBLEMS:

Nothing to report.

Changes in approach and reasons for change: N/A
Actual or anticipated problems or delays and actions or plans to resolve them: N/A
Changes that had a significant impact on expenditures: N/A
Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents: N/A
Significant changes in use or care of human subjects: N/A
Significant changes in use or care of vertebrate animals: N/A
Significant changes in use of biohazards and/or select agents: N/A

REPORTABLE OUTCOMES/PRODUCTS:

Publications, conference papers, and presentations

Journal publications.

Prevalence of Diagnosed Sleep Disorders and Sleep Related Procedures in Children with Autism Spectrum Disorders. Marilisa G. Elrod, Cade M. Nylund, Apryl L. Susi, Gregory H. Gorman, Elizabeth Hisle-Gorman, Derek J. Rogers, Christine Erdie-Lalena. Journal of Developmental and Behavioral Pediatrics [accepted]. Federal Support: Yes

Books or other non-periodical, one-time publications.

None

Other publications, conference papers, and presentations.

FY15 Abstracts

Jenny Jaskiewicz, Apryl Susi, Cade Nylund, Elizabeth Hisle-Gorman, Gregory Gorman, David Dennison, Christine Erdie-Lalena. Quantifying the Risks of Seizure Types in Autism. AAP National Conference and Exhibiiton, Washington, DC, Oct 24-27, 2015.

Christine Erdie-Lalena Apryl Susi MS, Cade Nylund, Gregory Gorman MD, Elizabeth Hisle-Gorman. Maternal, Prenatal, and Early Life Risk Factors for Autism. Society for Developmental and Behavioral Pediatrics 2015 Annual Meeting, Las Vegas, NV, October 2-5, 2015.

A Susi, E Hisle-Gorman, GH Gorman, C Erdie-Lalena, CM Nylund. Perforated Appendix and Children with Autism Spectrum Disorder. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [poster]

DJ Tolson, MG Elrod, CM Nylund, CR Erdie-Lalena. Psychotropic Medication Prescriptions in Children with Autism Spectrum Disorder. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [poster]

E Hisle-Gorman, A Susi, CM Nylund, CR Erdie-Lalena, DJ Tolson, GH Gorman. Mental Health Disorders and Psychiatric Medication Use in Children with Autism. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [poster]

Author(s): K Smith, GH Gorman, CM Nylund, A Susi, C Erdie-Lalena, E Hisle-Gorman. "Increased Rates of Injury in Children with Autism Spectrum Disorder." Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [poster]

*MG Elrod, CM Nylund, GH Gorman, E Hisle-Gorman, C Erdie-Lalena. Sleep Disorders and Sleep Related Procedures in Children with Autism Spectrum Disorder Diagnoses: A Retrospective Cohort Study Using the Military Health Systems Database. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [poster]

DJ Adams, A Susi, E Hisle-Gorman, C Erdie-Lalena, GH Gorman, M Rajnik, CM Nylund. Otitis Media and Related Complications among Children with Autism Spectrum Disorder Diagnoses. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [poster]

CM Nylund, A Susi, E Hisle-Gorman, C Erdie-Lalena, GH Gorman. Macronutrient and Micronutrient Malnutrition in Children with Autism Spectrum Disorder Diagnoses. Digestive Diseases Week, Washington, DC, May 2015 [poster]

K Shedlock, A Susi, E Hisle-Gorman, C Erdie-Lalena, GH Gorman, CM Nylund. Children with Autism Spectrum Disorder Diagnoses Have Elevated Risk of Obesity and Metabolic Comorbidities: A Retrospective Cohort Study Using the Military Healthcare Database. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [poster]

K Shedlock, A Susi, E Hisle-Gorman, C Erdie-Lalena, GH Gorman, CM Nylund. Children with Autism Spectrum Disorder Diagnoses Have Elevated Risk of Obesity and Metabolic Comorbidities: A Retrospective Cohort Study Using the Military Healthcare Database. Eastern Society for Pediatric Research Annual Meeting, Philadelphia, PA, March 22, 2015. [platform]

Nylund CM, Susi A, Hisle-Gorman E, Erdie-Lalena C, Gorman GH. Macronutrient and Micronutrient Malnutrition in Children with Autism Spectrum Disorder. Clinical Nutrition Week. Long Beach, CA Feb 2015 [platform]

CM Nylund A Susi, E Hisle-Gorman, C Erdie-Lalena, GH Gorman. Children with Autism Spectrum Disorder are More Likely to be Diagnosed with Celiac Disease. NASPGHAN (North American Society of Pediatric Gastroenterology, Hepatology and Nutrition) Atlanta, GA Oct 2014 [poster]

FY14 Abstracts

*Marilisa G. Elrod, Cade M. Nylund, Gregory H. Gorman, Elizabeth J. Hisle-Gorman, Christine Erdie-Lalena. Sleep Disorders and Sleep Related Procedures in Children with Autism Spectrum Disorder Diagnoses. Society for Developmental and Behavioral Pediatrics, Nashville, TN, Sept 2014.

Daniel J. Adams, Apryl Susi, Elizabeth Hisle-Gorman, Christine Erdie-Lalena, Gregory Gorman, Michael Rajnik, Cade M. Nylund. Otitis Media and Related Complications among Children with Autism Spectrum Disorder Diagnoses. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015

Cade M Nylund, Apryl Susi, Elizabeth Hisle-Gorman, Christine Erdie-Lalena, Gregory Gorman. Children with Autism Spectrum Disorder are More Likely to be Diagnosed with Celiac Disease. NASPGHAN (North American Society of Pediatric Gastroenterology, Hepatology and Nutrition) Atlanta, GA Oct 2014

*Cade M. Nylund, Apryl Susi, Elizabeth Hisle-Gorman, Christine Erdie-Lalena, Gregory Gorman. Macronutrient and Micronutrient Malnutrition in Children with Autism Spectrum Disorder Diagnoses. Digestive Diseases Week, Washington, DC, May 2015 [submitted]

*Katie Shedlock, Apryl Susi, Elizabeth Hisle-Gorman, Christine Erdie-Lalena, Gregory Gorman, Cade M. Nylund. Children with Autism Spectrum Disorder Diagnoses Have Elevated Risk of Obesity and Metabolic Comorbidities: A Retrospective Cohort Study Using the Military Healthcare Database. Pediatric Academic Society Annual Meeting, San Diego, CA, May 2015 [submitted]

*Theresa Heifert, Apryl Susi, Gregory H Gorman, Elizabeth Hisle-Gorman, Christine Erdie-Lalena, Cade M Nylund. Feeding disorders in children with autism spectrum disorders are related to a diagnosis of eosinophilic esophagitis. Digestive Diseases Week 2015, Washington, DC, May 17-19, 2015. [submitted]

FY 13 Abstracts

*Luis E. Lozada, Cade M. Nylund, Matthew D. Eberly, Elizabeth Hisle-Gorman, Anthony Goudie, Adam Huillet, Matilda Eide, Stephen L. Nelson, Christine Erdie-Lalena, Gregory H. Gorman, Devon Kuehn. Neonatal Hyperbilirubinemia as a Risk Factor for Autism Spectrum Disorder, a Retrospective Cohort Study. Pediatric Academic Society Annual Meeting, Washington D.C., May 6, 2013.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report.

PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

No change.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to report.

What other organizations were involved as partners?

Organization Name: Madigan Army Medical Center Developmental and Behavioral Pediatrics Fellowship

Location of Organization: Tacoma, WA

Partner's contribution to the project: two fellow trainees were primary authors on 2 projects

Financial support; None

In-kind support: None

Facilities: None

Collaboration: Two fellows worked on two individual projects.

Personnel exchanges: None

Other: None.

SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: N/A

QUAD CHARTS: N/A.

CONCLUSION:

The research group has assembled the largest cohort of children with autism spectrum disorder in one of the most comprehensive and longitudinal medical databases. The large size of this cohort has allowed quantification of common associations, medication burden, and co-morbid conditions, from sleep-related diagnoses, ear infections, celiac disease, appendicitis, injury rates, micronutrient deficiencies, malnutrition, obesity, obesity complications and more. Some of these conditions are relatively common, often go unnoticed due to the communication issues of ASD patients, or have a large impact on quality of patient and family life. The findings highlight the increased prevalence of these conditions which may be difficult to diagnose due to the communication difficulties in patients with ASD. Association findings can direct researchers to avenues of further inquiry into the etiologies of autism.

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APPENDICES:

Title: Maternal, Prenatal, and Early Life Risk Factors for Autism

Background: Autism spectrum disorders (ASD) are increasing in prevalence, however the cause remains unknown. An interplay between genetic and environmental factors is believed to impact risk, with the pre and perinatal periods understood to be especially important. We sought to examine the impact of maternal and child issues during pregnancy, birth and the first 90 days of life on the diagnosis of ASD.

Methods: 8,771 children diagnosed with ASD were matched to three controls by birthdate and gender. Maternal health records for one year preceding the birth of the child, birth records, and child health records for the first 90 days of life were extracted from the military health system database. Hierarchical logistic regression calculated odds of autism by 14 maternal, 4 birth and 7 child factors.

Results: Of the 25 included factors, there were 8 maternal, 3 birth, and 4 child level factors significantly associated with ASD diagnosed after the age of two. Significant factors that were most common were labor and pregnancy complications impacting 65% and 67 % of included mothers respectively. Maternal (0.6%) and fetal (0.8%) epilepsy were the least common of factors examined. ASD was most highly associated with seizure in the first 90 days of life, followed by maternal mental health diagnoses, epilepsy and obesity (Table 1).

Multiple maternal and child factors are associated with an increase odds of developing ASD. The highest increased risk was associated with newborn epilepsy suggesting that seizures early in life may be the earliest indicator of ASD.

Title: **Autism Spectrum Disorders and Metabolic Complications of Obesity**

Authors: Katherine Shedlock, MD[1]; Apryl Susi, MS[2]; Gregory Gorman, MD[2]; Elizabeth Hisle-Gorman, PhD[2]; Christine R. Erdie-Lalena, MD[1]; and Cade M. Nylund, MD[2]

Abstract

Background/Objectives: Children with Autism Spectrum Disorders (ASD) are known to have an increased risk of obesity. We sought to confirm this risk of obesity and evaluate an association of ASD with type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia, and non-alcoholic fatty liver disease/steatohepatitis (NAFLD/NASH). We also sought to evaluate the rates of prescribed treatment for obesity-related disorders, as well as determine if there is an association of treatment with psychotropic medications and the development of obesity for children with ASD.

Methods: A retrospective 1:5 case-cohort study was performed from October 2000 to September 2013 using the Military Health System database. For children with ASD and matched controls, ICD-9-CM diagnostic codes for obesity, T2DM, hypertension, hyperlipidemia, NAFLD/NASH, and prescriptions were obtained. Conditional logistic regression determined odds ratios and 95% confidence intervals.

Results: 48,762 individuals with ASD and 243,810 matched controls were identified. Children with ASD had significantly higher odds of having obesity (OR, 1.85; 95% CI, 1.78-1.92), having the obesity-related disorders, and being prescribed a medication when they had these diseases. In children with ASD, mood stabilizers, anti-psychotics, anti-epileptics, and SSRIs were associated with obesity.

Conclusions: Children with ASD have an increased risk of obesity and obesity-related metabolic disorders. They are more likely to be prescribed medications to treat these complications, suggesting they may have more severe disease. There is a significant association between the use of some psychotropic categories and a diagnosis of obesity, suggesting that obesity in children with ASD may be partially iatrogenic.

Prevalence of Diagnosed Sleep Disorders and Sleep Related Procedures in Children with Autism Spectrum Disorders

Marilisa G. Elrod, MD PhD[1], Cade M. Nylund, MD[2], Apryl L. Susi, MS[2], Gregory H. Gorman, MD[2], Elizabeth Hisle-Gorman, PhD[2], Derek J. Rogers, MD[3], Christine Erdie-Lalena, MD[3]

ABSTRACT

Objective: Sleep disorders are common and important comorbid conditions in children with autism spectrum disorders (ASD) and can cause cognitive and behavioral problems. Sleep disordered breathing (SDB) is a diagnosable and treatable cause of behavioral problems in children. We aimed to quantify the relative risk for children with ASD of being diagnosed with sleep disorders including SDB and undergoing sleep related procedures (SRP). **Method:** This retrospective case-cohort study included 48,762 children with ASD aged 2-18 years enrolled in the Military Health System (MHS) database from 2000- 2013. Children with ASD were matched 1:5 by birthdate, gender, and enrollment time to children without an ASD diagnosis. The MHS database was queried for International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for sleep disorders or ICD-9-CM and Current Procedural Terminology codes for SRP. Relative risks (RR) and 95% confidence intervals (CI) were determined with conditional Poisson regression. **Results:** Children with ASD were at higher risk of receiving any sleep disorder diagnosis (RR 1.97 [95% CI 1.91, 2.02]) including SDB (RR 1.96 [95% CI 1.88, 2.05]). Children with ASD also were at increased risk of undergoing sleep surgery (RR 1.50 [95% CI 1.46-1.54]), and polysomnography (RR 3.74 [95% CI 3.56- 3.93]). **Conclusion:** Children with ASD are more likely to be given a sleep disorder diagnosis including SDB and are more likely to undergo SRPs compared to controls without ASD.

Macronutrient and Micronutrient Malnutrition in Children With Autism Spectrum Disorder

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Pediatrics, Uniformed Services University of the Health Sciences, Bestheda, MD

Purpose: Autism spectrum disorder (ASD) represents a range of developmental disabilities that commonly affect behavior and sensory defensiveness related to eating and nutritional intake. Children with ASD have been shown to have self-selected, narrow dietary preferences and a preference for less nutritious snack foods. Feeding disorders and use of supplemental enteral nutrition are also common in children with ASD. Using the Military Health System (MHS) database, we sought to determine the prevalence of diagnosed malnutrition including specific micronutrient deficiencies in children with ASD, relative to those children without an ASD diagnosis.
Methods: This retrospective matched cohort study included subjects enrolled in the MHS database, which is comprised of data on outpatient visits and inpatient admissions of all military members and dependent children treated in military and civilian medical facilities. Children aged 2 to 18 years with ASD were classified by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9- CM) codes for an ASD diagnosis from October 1, 2003 to Jun 30, 2012 at two separate clinical encounters. The cases also were enrolled in the MHS database 6 months prior to receiving the first ASD diagnosis code and 6 months following receipt of the diagnosis. Five controls were matched without replacement to each case by age, gender, and enrollment timeframe. The database was queried for a variety of malnutrition and nutrient deficiency diagnoses utilizing ICD-9-CM codes for each subject and control during the specified period. Conditional logistic regression was performed with odds ratios (OR) with 95% confidence intervals (95% CI).
Results: The MHS dataset yielded 48,810 individuals with ASD and 240,282 controls. The percentage of children receiving any diagnosis of malnutrition during enrollment within the study timeframe was 16.3% for the ASD group and 6.8% for the controls. The frequencies and ORs are presented in Table 1. The most common diagnosis was Underweight/Loss of Weight (10.8% of children with ASD vs. 3.4% in controls). The most common micronutrient deficiency was iron deficiency anemia (4.1% of the children with ASD vs. 2.8% in controls). Consistent with a restrictive diet, the nutrient deficiencies most strongly associated with ASD were vitamin A deficiency (OR, 22.50; 95 % CI, 14.71-34.41), calcium (OR, 7.92; 95% CI, 6.17-10.16) and folate (OR, 5.29; 95% CI, 2.73-10.72).
Conclusions: Diagnosed macro- and micronutrient deficiencies are very common in children with ASD, with 1 in 5 having at least one malnutrition diagnosis. Diets deficient in vegetables or dairy correspond to the specific nutrient deficiencies found in children with ASD in this study. These results represent only diagnosed deficiencies, however, and likely underrepresent the actual portion of malnourished children with ASD. Children with ASD are at nutritional risk and warrant nutrition-focused health supervision.

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Quantifying the Risks of Seizure Types in Autism

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ABSTRACT

OBJECTIVE: Children with autism are known to have increased rates of epilepsy. Prevalence rates vary widely. Past studies aimed to quantify these rates are small. This study aims to determine whether and how much more likely children with autism are to be diagnosed with a specific seizure problem including status epilepticus, infantile spasms and petit mal (absence) seizures.

METHODS: A retrospective matched case cohort study was performed. We identified pediatric patients 0-18 years of age in the Military Health System database between 2000-2013. Children with ASD were matched 1:5 to children without ASD by birthdate, gender, and enrollment time. ICD9 diagnosis codes were used to identify patients. Conditional logistic regression was used to calculate the odds of varied seizure types.

RESULTS: 48,762 ASD patients were identified and matched to 243,810 controls. For autistic children, the odds ratio (OR) of having some kind of seizure or seizure disorder was 6.03 (95% CI; 5.84-6.22). This represented 19% of the patients with autism. In a subgroup analysis of patients with status epilepticus the OR was 8.00(CI 7.11-8.99). The OR of patients of absence seizures was 9.54(CI 8.76-10.38). The OR of patients with infantile spasms was 7.30 (CI 5.74-9.28). Although the OR of febrile seizures was significant, it was far less so (OR 2.19 (CI 2.05-2.33).

CONCLUSIONS: This study helps to quantify the percentage of autistic patients with seizures, and different seizure types. Rates of epilepsy in children with autism are vastly increased in a wide variety of seizure types, known to have different etiologies, genetic and otherwise.

Increased Rates of Injury in Children with Autism Spectrum Disorder

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Abstract

Background and Objectives: Children with Autism Spectrum Disorders (ASD) exhibit behaviors that increase injury risk. Our objective was to identify rates of injury in children with ASD after controlling for common comorbidities.

Design/Methods: A retrospective matched case-cohort was formed from children aged 2-18 years enrolled in the Military Healthcare System in 2000-2013. Children with diagnosed ASD were matched 1:5 on age, gender, and enrollment time. ASD and injuries were identified by ICD-9-CM codes.. Conditional Poisson regression analysis, adjusting for diagnosed epilepsy and ADHD determined incidence rate ratios (IRR) of injuries.

Results: The case-cohort consisted of 48,762 children with ASD and 243,810 controls. Children with ASD had more encounters for injury than controls (IRR 1.17 [95%CI 1.15-1.19; p<0.001]). After adjusting for ADHD and epilepsy, children with ASD had a lower overall injury rate. ASD was shown to associated with specific injury sub-types including burns, poisonings, surgical complications and environmental/inflicted injuries. For children with ASD, additional comorbid diagnoses conferred increasing injury risk. Children with ASD alone had an IRR of 1.04 (95%CI 1.03-1.05; p<0.001), children with ASD and ADHD had an IRR of 1.20 (95%CI 1.19-1.20; p<0.001), children with ASD and epilepsy had an of IRR of 2.60 (95%CI 2.55-2.65; p<0.001), and children with ASD, epilepsy and ADHD had an IRR of 2.03 (95%CI 2.00-2.06; p<0.001).

Conclusions: Children with ASD are at increased risk of poisoning, burns, surgical complications and environmental/inflicted injuries. Coexisting ADHD and epilepsy confer the highest injury risk. Targeted injury prevention should be provided for children with ASD.

Mental Health Disorders and Psychiatric Medications Use in Children with Autism

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Background: Small studies suggest high rates of mental health co-morbidities in children with autism spectrum disorders (ASD). Large studies comparing mental health co-morbidities and associated medication use have not been completed.

Objective: To determine the prevalence of mental health diagnoses and psychiatric medication use in children with ASD.

Methods: A retrospective matched case cohort of children aged 2-18 years enrolled in the Military Healthcare System (MHS) in 2000-13 was formed. 48,762 children with two or more visits for ASD were categorized cases, and matched 1:5 to children without ASD. Mental health diagnoses as categorized by AHQR were identified by ICD-9 code. Psychiatric medications were identified by American Hospital Formulary Service therapeutic class codes. Conditional logistic regression calculated odds of a mental health comorbidity. Non-parametric methods compared days of medication use.

Results: 39,088 children with ASD (80.2%) had one or more mental health diagnosis as compared with (30.3%) of controls. Children with ASD had a mean of 2.2 mental health conditions compared to 0.55 in children without ASD. Attention deficit, mood and adjustment disorders were most common mental health diagnosed in children with ASD. The odds of being diagnosed with all mental health condition studied were increased in children with ASD (Table1). Psychiatric medication use was greatly increased in children with comorbid ASD and mental health conditions (Table 2).

Conclusion: The majority of children with ASD have concurrent mental health conditions, and are more likely to have multiple conditions compared with controls. Children with ASD and comorbid mental health conditions have increased use of psychiatric medications.

Psychotropic Medication use in Military Children with Autism Spectrum Disorder: A Retrospective Cohort Comparison Using the Military Health System Database

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Abstract:

Background: The use of behavior altering medication in children with Autism Spectrum Disorder (ASD) has increased over time. While the etiological search for Autism continues many families are turning to medications to help manage children's behaviors.

Objective: To assess psychotropic medication burden among a geographically and economically diverse set of children with ASD as compared to a matched set of controls. We further sought to understand the impact of co-morbid diagnoses on medication use in children with ASD.

Methods: A retrospective matched cohort study was used to compare psychotropic, anti-epileptic and sleep medication prescriptions data for children aged 2-18 years old enrolled in the Military Health System (MHS) between 2000 and 2013. Children with ASD, mental health conditions, sleep disorders and epilepsy were identified by ICD-9 code. Five controls were matched without replacement to each child with ASD by age, gender, and enrollment time. Odds ratios compared types of medications and Conditional Poisson regression compared medication days and medication type by ASD and the impact of common ASD comorbidities on medication use.

Results: Of 48,810 children with ASD 31,841 (65%) were prescribed a psychotropic medication as compared to 45,740 of 244,045 controls (19%). ASD conferred increased medication use in children with mental health conditions (IRR 3.97 [3.97-3.97]), sleep disorders (IRR 5.55 [5.35-5.77]) and epilepsy (IRR 2.56 [2.40-2.74]). For children with ASD having a mental health condition increased medication days over 12 times (IRR 12.95 [12.92-12.99]) as compared to children with ASD and no comorbid conditions, and children with epilepsy and sleep disorders had over 32 times as many medication days (IRR 32.56 [32.47-32.65]).

Conclusion: ASD and its comorbidities greatly increases the medication burden in children. As compared to controls with ASD and no comorbidities, and children with mental health, epilepsy or sleep disorders alone, children with ASD and a diagnosed comorbid condition have a drastically increased medication burden.